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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

DAHIYAT et al.

Serial No. 09/574,443

Filed: May 19, 2000

For: NOVEL PROTEINS WITH  
INSULIN-LIKE ACTIVITY  
USEFUL IN THE TREATMENT  
OF DIABETES

Examiner: SAOUD, C.

Group Art Unit: 1646

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, DC 20231 on:

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Mary McFarland

Assistant Commissioner of Patents  
Washington, DC 20231

**RESPONSE TO RESTRICTION AND PRELIMINARY AMENDMENT**

Sir:

This paper is being submitted in response to the Restriction Requirement mailed March 15, 2002. The response is accompanied by a petition for a two-month extension of time, the required fee, and is filed on or before the due date of 17 June 2002, the first business day after Saturday 15 May 2002, making this a timely response. The Commissioner is authorized to charge any additional fees, including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-68064-1/RFT/RMS/RMK).

In response to the Restriction Requirement, Applicants elect for further prosecution the claims of Group I, namely Claims 1-17, drawn to proteins. This election is made without traverse.

In addition, Applicants are additionally required to elect a protein to be examined. Applicants elect the protein defined by SEQ ID NO: 7. ***This election is made with traverse.***

Claims 1-17 and newly added claim 22 are readable on the elected invention. In addition, Applicants respectfully ask the Examiner to consider newly added claims 23-29, drawn to computational methods of making IA proteins.

Prior to examination, please amend the above-identified application as follows:

**In the Specification:**

Please replace the paragraph beginning at page 39, line 17, with the following rewritten paragraph:

B1  
--Thus, in one preferred embodiment, PDA design is used to generate IA proteins that promote hexamer formation, but occlude phenol binding. In one aspect of this embodiment, IA proteins are generated that are stable and form hexamers in the absence of phenolic preservatives. Some of these IA proteins may form hexamers that are more stable than the human insulin bound to a phenolic compound. In this embodiment, the PDB entry 1waw was chosen. For the PDA calculation, the entire insulin hexamer complex, consisting of 6 A-chains (chains 1, 3, 5, 7, 9, and 11 in hexamer) and 6 B-chains (chains 2, 4, 6, 8, 10, and 12 in the hexamer) was used.--

**In the Claims:**

✓ Please cancel 18-21 without prejudice or disclaimer as drawn to a non-elected invention.

Please amend the following claims:

Sub C1  
B2  
1. (Amended) A non-naturally occurring insulin activity (IA) protein comprising an amino acid sequence which comprises substitution of at least one amino acid residue when compared to an amino acid sequence of a naturally occurring human insulin and wherein said IA protein has an altered property when compared to the same property of human insulin and binds to a cell comprising an insulin receptor.

B3 Sub D4  
10. (Amended) The non-naturally occurring IA protein according to claim 1 wherein said IA protein comprises an amino acid sequence selected from the group of amino acid sequences shown in Figure 3A (SEQ ID NO: 7), Figure 3B (SEQ ID NO: 8), Figure 3C (SEQ ID NO: 9), Figure 3D (SEQ ID NO: 10), Figure 3E (SEQ ID NO: 11), Figure 3F (SEQ ID NO: 12), Figure 3G (SEQ ID NO: 13), Figure 4A (SEQ ID NO: 14), Figure 4B (SEQ ID NO:

B3  
15), Figure 4C (SEQ ID NO: 16), Figure 4D (SEQ ID NO: 17), Figure 4E (SEQ ID NO: 18), Figure 4F (SEQ ID NO: 19), Figure 4G (SEQ ID NO: 20), Figure 5A (SEQ ID NO: 21), Figure 5B (SEQ ID NO: 22), and Figure 5C (SEQ ID NO: 23).

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Please add the following new claims:

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--22. A non-naturally occurring IA protein according to claim 10 wherein said IA protein comprises the amino acid sequence shown in Figure 3A (SEQ ID NO: 7).

23. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- B4
- a) receiving a protein backbone structure of an insulin activity (IA) protein with variable residue positions;
  - b) selecting a set of variable positions;
  - c) establishing a group of potential rotamers for each of said variable residue positions;
  - d) analyzing the interaction of each of said rotamers in each group with all or part of the remainder of said protein to generate a set of optimized protein sequences.

24. A method according to claim 23, wherein said analyzing step further comprises the use of at least one scoring function.

25. A method according to claim 23 wherein said IA protein is a wild-type IA protein.

26. A method according to claim 23 wherein said wild-type IA protein is a mammalian insulin species selected from the group consisting of bovine (GenBank accession number IPBO), dog (GenBank accession number IPDG), sheep (GenBank accession number INSH), cat (GenBank accession number INCT), pig (GenBank accession number IPPG), mouse (GenBank accession numbers INMS1 and INMS2), rat (GenBank accession numbers IPRT1 and IPRT2), horse (GenBank accession number IPHO), rabbit (GenBank accession number INRB), guinea pig (GenBank accession number IPGP), hamster (GenBank accession number INHY), goat (GenBank accession number INGT), chimpanzee (GenBank accession number A42179), and green monkey (GenBank accession number B42179).